
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Michels and zur Hausen misquote Elbasha and colleagues[4] as saying that inclusion of men in HPV vaccination programmes is "the most cost-effective approach". Even the models in that paper indicate that vaccinating men, at significant additional cost, would produce only a modest gain in quality-adjusted life-years. This was the *least* cost-effective strategy. Furthermore, a systematic review[5] of economic models concluded that: "Studies had a consistent message... a male and female [HPV] vaccination programme is generally not cost effective compared with female-only vaccination."

Given the challenges that developing countries face, available resources should focus on the most effective, efficient, and affordable immunisation intervention: vaccinating girls before sexual debut.

We declare that we have no conflicts of interest.

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2 Ault KA. Long-term efficacy of human papillomavirus vaccination. *Gynecol Oncol* 2007; **107:** S27–30.
3 Goldie S. A public health approach to cervical cancer control: considerations of screening and vaccination strategies. *Int J Gynaecol Obstet* 2006; **94:** S95–105.
4 Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. *Emerg Infect Dis* 2007; **13:** 28–41.
5 Marra F, Cloutier K, Oteng B, Marra C, Ogilvie G. Effectiveness and cost effectiveness of human papillomavirus vaccine: a systematic review. *Pharmacoeconomics* 2009; **27:** 127–47.

Karin Michels and Harald zur Hausen[1] discuss the results of the adjuvanted human papillomavirus (HPV) vaccine trial by J Paavonen and colleagues[2] and conclude that men and boys, as well as women and girls, should be vaccinated. Although the study findings bode well for both eventual effectiveness in select populations and broader-spectrum protection, the report suggests that vaccination of women with previous HPV 16 or 18 infection might actually increase their risk of high-grade cervical disease—an observation strikingly consistent with reports on the quadrivalent HPV vaccine.[3]

Although each trial's finding was attributed to imbalances in the baseline characteristics of the vaccine and placebo groups, the biological phenomenon of antibody-dependent enhancement of disease should be considered.[4,5] These clinical trials include thousands of vaccinees previously exposed to HPV 16 or 18; those women could be studied further with appropriate comparison groups. Cross-protection data in Paavonen and colleagues' study[2] suggest that such investigations should include women with baseline HPV 31, 33, or 45.

What if HPV vaccination were contraindicated for women and girls previously infected? It might be argued that, in ideal settings, increased disease risk in a minority of vaccinees would be managed by the safety net of continued cervical cancer screening. Or perhaps HPV testing could precede vaccination. For developing nations, where a vaccine is most needed, such logic disintegrates. Furthermore, restricting vaccinations to prepubescent girls might be particularly prudent in the developing world. Young or old, a woman's previous infection risk can be difficult to ascertain, particularly in cases of unacknowledged rape or other sexual molestation.

Although the global eradication of HPV infection is a noble goal, we currently have neither sufficient evidence nor the requisite understanding of the immunology of HPV infection to suggest HPV vaccination for all.[1]

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2 Paavonen J, Naud P, Salmeron J, et al, for the HPV PATRICIA Study Group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009; **374:** 301–14.
3 Vaccine and Related Biological Products Advisory Committee. VRBPAC background document: Gardasil HPV quadrivalent vaccine.http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222B3.pdf (accessed July 20, 2009).
4 Tirado SMC, Yoon K-J. Antibody-dependent enhancement of virus infection and disease. *Viral Immunol* 2003; **16:** 69–86.
5 Huisman W, Martina BE, Rimmelzwaan GF, Gruters RA, Osterhaus AD. Vaccine-induced enhancement of viral infections. *Vaccine* 2009; **27:** 505–12.

## Authors' reply

Unlike Vivien Tsu and Scott Wittet, we are indeed convinced that life-long immunity after human papillomavirus (HPV) vaccination is unlikely and question the relevance of mathematical models based on hepatitis B vaccination. Results from long-term follow-up are not yet available, and it remains to be seen whether a quadrivalent or bivalent HPV vaccine will elicit a response similar to that produced by a monovalent hepatitis B vaccine. Additionally, it is very likely that the observed weak cross-reactivity with types 31, 33, and 45 will require a booster injection after 10–15 years, given the current vaccination protocol.

We disagree with Tsu and Wittet's contention that cervical cancer is a public health problem but that HPV infections are not. It would be short-sighted to disregard the large number of cervical lesions that develop after infections with high-risk HPV types requiring surgical interventions. Since cervical cancer is caused by HPV infections, the most effective strategy to prevent this cancer, its precursor lesions, and the associated pain and suffering is the prevention of infection.

Elbasha and colleagues[1] found that inclusion of men and boys in the vaccination programme was more effective than inclusion of only girls

and women, "reducing the incidence of genital warts, cervical intraepithelial neoplasia, and cervical cancer by 97%, 91%, and 91%, respectively". Although the initial expense will be higher, additionally accounting for the prevention of HPV-linked cancers in men (eg, anal, penile, and oropharyngeal cancers) will make this approach cost effective. The eventual eradication, or even a drastic reduction in the rate of HPV infections, will require vaccination of both sexes.

The results of HPV vaccination of people with previous HPV 16 or 18 infection have to be interpreted with caution. Contrary to what Michele Manos suggests, any differences in cervical intraepithelial neoplasia of grade 2 or above (CIN2+) between vaccinated and non-vaccinated women were non-significant, and only 3% of the study population was both HPV 16/18 DNA-positive and seropositive.[2,3]

Antibody-dependent exacerbation of viral infections seems to mainly concern specific RNA viruses, such as feline coronavirus, dengue virus, and feline immunodeficiency virus.[4] Currently, there is little evidence that antibody-dependent exacerbation facilitates HPV infection, particularly since the presently available vaccines against high-risk HPV types seem to neutralise viral particles before cell entry.

Although Manos considers the eradication of HPV infections a "noble goal", the development of HPV vaccines was unnecessarily delayed by doubts about the causal role of HPV infections in cervical cancer.[5] We do not have to wait for more detailed immunological studies before we start planning large-scale interventions, since they will be highly effective public health programmes. Without a strategic vision, global programmes will not be started.

We declare that we have no conflicts of interest.

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1 Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. *Emerg Infect Dis* 2007; **13:** 28–41.
2 Paavonen J, Naud P, Salmerón J, et al, for the HPV PATRICIA Study Group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009; **374:** 301–14.
3 Vaccine and Related Biological Products Advisory Committee. VRBPAC background document: Gardasil HPV quadrivalent vaccine. http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222B3.pdf (accessed Sept 30, 2009).
4 Huisman W, Martina BE, Rimmelzwaan GF, Gruters RA, Osterhaus AD. Vaccine-induced enhancement of viral infections. *Vaccine* 2009; **27:** 505–12.
5 zur Hausen H. Cervical carcinoma and human papillomavirus: on the road to preventing a major human cancer. *J Natl Cancer Inst* 2001; **98:** 250–53.

## Expanding HIV care in Africa: making men matter in Johannesburg

In their Viewpoint (July 25, p 275),[1] Edward Mills and colleagues highlight the need to provide HIV testing and treatment services that are more accessible to men. As they note, men make less use of routine health services than women, partly because such services are often not easily accessible to those who are employed.

In South Africa, we have established services that provide screening, care, and treatment for HIV that target inner-city workers. The Emthonjeni centre is based in central Johannesburg at a large taxi rank used by an estimated 400 000 commuters daily. It provides screening for HIV and tuberculosis, along with blood pressure and glucose checks, and is convenient for commuters and those employed locally. Currently, those found HIV-positive are referred to nearby general practitioners with extended opening hours who provide HIV care and treatment; we plan to extend our services to provide HIV care on site. Taxi drivers are encouraged to be "ambassadors", promoting Emthonjeni services to their passengers. Additionally, Emthonjeni mobile units similarly provide screening to small (<100 employees) inner-city enterprises whose staff rarely have medical insurance.

Between March, 2008, and May, 2009, 14 494 people (57% men) were tested for HIV and received their results, of which 2432 (17%) were positive. 1784 of these are now in HIV care and 1069 have started antiretroviral therapy. We believe that initiatives like ours have potential to promote knowledge of HIV status among men and facilitate earlier access to antiretroviral therapy, thus reducing mortality.

We declare that we have no conflicts of interest.

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1 Mills EJ, Ford N, Mugyenyi P. Expanding HIV care in Africa: making men matter. *Lancet* 2009; **374:** 275–76.

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## The missing ingredient in medicine patent pools

In response to your Editorial (July 25, p 266),[1] we do not find it any more surprising that pharmaceutical companies do not support the UNITAID patent pool, backed by nongovernmental organisations (NGOs), than the fact that NGOs give lukewarm support to GlaxoSmithKline's patent pool over neglected diseases. The pharmaceutical industry and NGOs have been vying for leadership over the issue of access to medicines in competition, rather than in cooperation, with one another.[2]